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Published in:
Europace

Publication date:
2010

Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Tilburg University Research Portal](#)

Citation for published version (APA):
Duru, F., Dorian, P., Favale, S., Perings, C., Pedersen, S. S., & Willems, V. (2010). Effects of an alert system on implantable cardioverter defibrillator-related anxiety: Rationale, design, and endpoints of the PANORAMIC multicentre trial. *Europace*, 12(5), 726-730.

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Effects of an alert system on implantable cardioverter defibrillator-related anxiety: rationale, design, and endpoints of the PANORAMIC multicentre trial

Firat Duru^{1*}, Paul Dorian², Stefano Favale³, Christian Perings⁴, Susanne S. Pedersen⁵, and Vincent Willems⁶ on behalf of the PATient NOTifier Feature for Reduction of Anxiety: A Multicenter ICD Study (PANORAMIC) investigators

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Received 4 November 2009; accepted after revision 19 January 2010

Aims

Implantable cardioverter defibrillators (ICD) can prevent sudden cardiac death by delivering high-energy shocks in patients at risk of life-threatening ventricular tachyarrhythmias. Patients may be anxious about receiving inappropriate shocks in case of device or lead system malfunction, or about failing to receive needed therapy for the same reason. New devices include programmable vibrating patient notifiers (PN), which, by warning patients of a possible device

ICD study (PANORAMIC) is a multicentre, randomized, clinical trial designed to examine the effects of the awareness of an active vibrating alert system on device-related anxiety.

Methods

The trial will randomly assign 356 patients in a 1:1 design to a control group (PN OFF) vs. a treatment group (PN ON). Patients will be followed for 12 months, with visits scheduled at 6 and 12 months. During clinical follow-up visits, the ICD will be interrogated, and all patients will complete the Hospital Anxiety and Depression Scale and a device-related anxiety questionnaire. The sensitivity and specificity of PN, the effect of personality on anxiety, using the Type D scale (DS14), the number of delivered appropriate and inappropriate ICD therapies, changes in anxiety related to the delivery of appropriate or inappropriate shocks, crossovers from the assigned group, the number of hospitalizations, and the mortality rate will also be assessed.

ClinicalTrials.gov Identifier: NCT00559559.

Keywords

Implantable cardioverter defibrillator • Defibrillator shock • Patient notifier • Anxiety disorder

Introduction

In selected patients at high risk of life-threatening ventricular tachyarrhythmia, implantable cardioverter defibrillators (ICD) lower the risk of sudden cardiac death by delivering therapeutic electrical shocks.^{1,2} However, the life-saving delivery of ICD therapy is often painful and unpredictable,³ and can cause anxiety and concerns with respect to proper device function.^{4–11} Patients may be anxious about receiving inappropriate shocks in case of device or

lead system malfunction, or about failing to receive needed therapy for the same reason. These concerns can arise before the therapy is delivered, but may be greater after inappropriate or appropriate shocks. New devices are able to alert patients in case of device malfunction, a new feature that might help in the management of anxiety associated with the implantation of cardiac devices. The patient notifier™ (St. Jude Medical, Sylmar, CA) is such a new feature, designed to vibrate, thereby warning patients of possible device malfunction. The PATient NOTifier feature for Reduction of

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Anxiety: a Multicentre ICD trial (PANORAMIC) was designed to test the hypothesis that the PN™ might significantly decrease the device-related anxiety of ICD recipients.

Study design

PANORAMIC is an international, multicentre, randomized, open, parallel trial designed to test the hypothesis that the awareness of the activation of PN decreases device-related anxiety in ICD recipients at 12 months following device implantation. Patients will be enrolled over a 24-month period and followed for 12 months. All patients included in this study will be recipients of an ICD manufactured by St Jude Medical, equipped with PN. After enrolment and baseline evaluation, patients will be randomly assigned in a 1:1 design to a control (PN OFF) vs. a treatment (PN ON) group (Figure 1). To create similar study groups with respect to baseline characteristics and eliminate possible patient biases, the randomization procedure will use an evenly distributed table with permuted blocks. The study inclusion and exclusion criteria are listed in Table 1.

The patient information at the time of study inclusion has been standardized to inform the patients of the available vibration feature that automatically alerts the patient in case a device-related event may occur. The patients are also informed that the impact of this feature on patient anxiety has not been systematically studied to date. ICD patients who perceive vibration alerts are instructed to contact the ICD clinic as soon as possible, with no need to seek for emergency medical contact if they are feeling well.

Study endpoints

The main objective of PANORAMIC is to determine whether PN significantly decreases device-related anxiety in ICD recipients. The reduction in device-related anxiety in both groups will be measured at 12 months and compared with the measurement made at the time of enrolment, using Questions 9 and 10 of a questionnaire developed by Duru et al.⁸ (Table 2). The question-

aspects of device therapy, such as perception of the device, technical concerns, and individual patient needs. Additional longitudinal

Table 1 Study inclusion and exclusion criteria

Inclusion criteria
Implantation of an ICD with PN within 2 weeks to ≤14 weeks
Willingness and ability to understand and complete independently the study-related questionnaires
Signed informed consent form
Exclusion criteria
Age <18 years
PN alert received prior to study enrolment
Prior pacemaker or ICD implant
Patient in hospital or on transplantation list since ICD implant
Major mental illness or cognitive impairment
Unable to comply with follow-up schedule
Life expectancy <1 year
Pregnant state

comparisons where each patient serves as his/her own control at the time of randomization will be performed.

Additional data

Additional measurements which have been planned as part of this study are as follows (i) sensitivity and specificity of PN, (ii) changes in overall anxiety ascertained by the Hospital Anxiety and Depression Scale (HADS¹²), (iii) time-dependent changes in anxiety stratified by personality types as ascertained by the Type D scale (DS14¹³), (iv) number of appropriate and inappropriate ICD therapies, (v) changes in anxiety attributable to the delivery of appropriate and inappropriate shocks, (vi) crossovers from the assigned to the alternate randomization group, (vii) number of hospitalizations, and (viii) mortality rate. Additional data that will be collected at baseline and during follow-up, and compared between the two study groups are listed in Table 3.

Device description

This study will include recipients of single chamber, dual chamber, and cardiac resynchronization therapy (CRT-D) devices (Epic® II, Atlas® II, or subsequent ICD models) manufactured by St. Jude Medical, equipped with PN, a new function that gently vibrates to alert the patient of possible device malfunction, allowing the patient to expeditiously inform the caregivers. The device can be programmed to notify the patient if any of the following conditions occur:

- Device at elective replacement indicator (ERI): The unloaded battery voltage has reached the ERI voltage.
- Charge time limit reached: The high-voltage capacitors have not reached the programmed voltage within 28 s.
- Possible HV circuit damage: The device circuitry may be damaged.
- Device reset: A software reset has occurred.
- Back-up VVI: The device has experienced a hardware reset.
- Lead impedance out of range: The atrial and/or ventricular lead impedance is out of range (<200 or >2000 Ω). For CRT-D

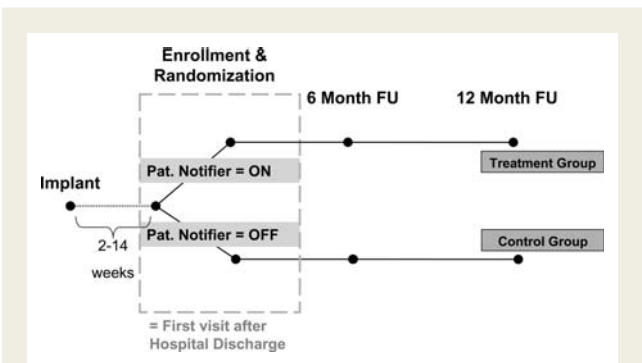


Figure 1 Patient NOTifier feature for Reduction of Anxiety: a Multicentre ICD trial design.

Table 2 Device-specific questionnaire

Questions	Answer categories
1. To what extent do you feel physically limited by your ICD?	No limitation/minor limitations/marked limitations/disabled
2. How often do you think about your ICD?	Never/occasionally/often/daily
3. Did you feel depressed when you were informed of the need to implant an ICD?	No/somewhat/moderately/markedly
4. Since the ICD implant, how preoccupied are you with your heart condition?	Not at all/mildly/markedly/obsessed
5. Did the ICD change your body image?	Yes/no
6. How disturbed are you by the visible changes at the site of ICD implantation?	Not disturbed/mildly/moderately/markedly
7. Does the ICD interfere with your daily life?	No/a little/moderately/markedly
8. Does the ICD interfere with your leisurely activities?	No/somewhat/moderately/markedly
9. Are you concerned about premature end of life of your ICD battery?	No/somewhat/moderately/very
10. Are you concerned about possible malfunctions of your ICD?	No/somewhat/moderately/very
11. How thoroughly has your ICD been explained to you?	Not explained/somewhat thoroughly/thoroughly/very thoroughly
12. How well are you informed about your heart disease?	Not informed/superficially/in depth/extensively
13. Do you perceive the ICD as a source of security?	No/somewhat/definitely
14. Do you expect the ICD to prolong your life?	No/somewhat/moderately/markedly
15. Is the ICD a source of anxiety for you?	No/somewhat/moderately/markedly
16. Would you like more frequent appointments with your physician?	Yes/no
17. Would you like longer appointments with your physician?	Yes/no
18. Would you like to have psychological or psychotherapeutic support?	Yes/no
19. Would you like to participate in a support group?	Yes/no
20. Should the public be better informed about implantable devices for heart diseases?	Yes/no
21. How do you feel compared with before the ICD implantation?	Worse/the same/better
22. How long did it take you to adjust to the ICD?	<1 month/up to 6 months/up to 1 year/not adjusted
23. Overall, was it worthwhile having the ICD implanted?	No/probably/definitely

Table 3 Additional study data

Lowering of general anxiety, assessed by the Hospital Anxiety and Depression Scale
Time-dependent changes in anxiety (assessed with the study questionnaires) for different personality types, assessed by the Type D scale (DS14)
Changes in anxiety related to the delivery of appropriate or inappropriate shocks
Crossovers from the randomly assigned group
Sensitivity and specificity of PN
Number of appropriate ICD therapies
Number of inappropriate ICD therapies
Number of hospitalizations
Mortality rate

devices, the lead impedance for the right- and left-ventricular leads is programmed and monitored independently.

- Out of range of the high-voltage lead impedance (HVLI)*: HVLI is measured on a daily basis; the HVLI exceeds a programmable upper or lower limit.
- Over current detection*: Safety feature that monitors for an electrical short in the device circuitry and defibrillation lead system.

*Only available for currentTM, promoteTM and subsequent devices onwards.

In patients randomly assigned to the PANORAMIC treatment group, all PN alerts will be activated.

Patient follow-up

Patients will be enrolled between 2 and 14 weeks after ICD system implantation during the first outpatient visit, which will be Day 0 of the trial. Early assessment of baseline anxiety during the initial hospitalization for implantation is not included, since factors such as surgery-related anxiety or the hospitalization for implantation itself may play a role as potentially confounding factors. After completion of the Duru questionnaire, HADS, and the DS14, patients will be randomly assigned to the treatment vs. control group. The patient's medical history and all prescribed cardioactive and mood-altering medications will be recorded. Systematic follow-ups are planned at 6 and 12 months after enrolment, at which time the patient will complete the Duru and HADS questionnaires again. The ICD will be interrogated, and the changes in the drug regimen recorded. Patients will be allowed to crossover to an alternate study group for medical reasons. The Duru and HADS questionnaires will be repeated before the crossing over of patients to an alternate study group.

Sample size calculation

The study sample size was calculated on the basis of the primary endpoints, using the scores of the Duru questionnaire in answers to questions pertaining to battery depletion- and device

malfunction-related anxiety. Assuming 10 and 15% improvements in anxiety scores in a mixed population of ICD patients without and with shocks, respectively, a total of 284 patients (142 per group) was calculated, using an unpaired *t*-test, to detect the difference with an 80% power at the one-sided 5% significance level. Further, assuming a dropout rate of 20%, a total recruitment of 356 patients has been planned.

Statistical analysis

The main analysis of the primary endpoints will be based on the intention-to-treat principle, comparing the randomly assigned groups and including all protocol deviators. A secondary per-protocol analysis of the primary endpoints will compare the groups as treatment actually received, excluding all major deviators. The primary analysis will be a logistic regression model, using change in anxiety score as response variable, and baseline anxiety score, treatment (PN ON vs. OFF), and centre as covariates. The result will be expressed as *P*-value derived from the likelihood ratio test or Wald χ^2 test. In addition, it will be investigated if the interaction between the centre and the treatment will have a significant effect on the response to improve the model fitting, and if so, the interaction term will be added in the model. Further univariate tests will be implemented for each covariate in order to gain an insight of the marginal association between the response and covariates. Taking the repeated measurements of the anxiety score into account, an additional generalized linear mixed model will be built, including anxiety score as response variable and baseline score, treatment, centre, delivery of shock (yes/no), Type D vs. non-Type D personality, participation in a patient support group or rehabilitation program, and engagement in a stable relationship as covariates. The statistical analysis will be performed using the SAS software, version 9.1 and NCSS version 2007.

Study questionnaires

Due to recent studies showing the influence of psychological factors, such as personality on anxiety,^{14–17} the patients will complete the DS14, stratifying the patient population into Type D (distressed) vs. non-Type D (non-distressed) patients. For the analyses of the Duru questionnaire,⁸ besides the primary analysis, the total score for Duru questionnaire will be analysed as well; for the HADS and DS14 questionnaires, subscale scores and personality types will be calculated according to previously validated scoring algorithms for the questionnaires.

Sensitivity and specificity calculations

The sensitivity and specificity of PN will be calculated according to the following definitions:

(i) True Alert: PN was perceived and the event was confirmed by the device; (ii) False Positive: PN was perceived and no event was recorded by the device; (iii) False Negative: PN was NOT perceived though an event was recorded by the device; (v) No Alert: An event was neither perceived nor recorded by the device. The

ratio, (ii) sensitivity/specificity, (iii) odds ratio, and (iv) 95% confidence limits for odds ratio will be calculated.

Steering committee

A study Steering Committee, consisting of the authors of this paper (with the exclusion of V. Willems), is in charge of (i) developing the protocol, (ii) monitoring its implementation, and (iii) ensuring the timely publication of the study results.

Discussion

The implantation of an ICD is a major life event, which may potentially change the patient's body image, interfere with psychosocial adaptation and quality of life, and promote the development of affective disorders. Several studies have examined the psychological impact of implanted cardiac devices, particularly with respect to depression and anxiety, focusing primarily on the presence or extent of affective disorders.^{3–11,13–17} While the latest ICDs are capable of monitoring device functioning and alerting the patient

device-related anxiety has not yet been examined.

The PANORAMIC trial was designed to evaluate the impact of a new, vibration-based PN warning system on anxiety related to the implantation of ICD. By using a vibratory notification, the PN distinguishes itself from other notifier systems with a tonal alert, which is often confused with environmental noise. If patients believe that they hear their device beeping, it could cause heightened anxiety through increased anticipation of receiving a tonal alert.

The Duru questionnaire will explore several specific components, including perception of the device, technical concerns, and device-related anxiety.⁸ Using this questionnaire in a group of device recipients previously revealed that patients who had received an ICD shock were more likely to perceive the device as life-saving, but also expressed greater anxiety regarding the possibility of future battery depletion and technical failures than ICD recipients who had received no shock.⁸ This might be explained by several contributing factors. ICD shocks delivered in the awake state, whether appropriate or inappropriate, may be traumatic and lead to anticipatory anxiety for further unpredictable shocks, including a persistent conflict between the fear of experiencing unpleasant shocks and that of dying suddenly. The incorporation of new functions to monitor proper device function and alert the patients in case of technical dysfunction may increase the overall patient well-being and lower anxiety. Additionally, patients with 'inappropriate' ICD shocks due to lead or system malfunction may be anxious about repeat device-related problems, and seek reassurance that these problems have not recurred.

Several additional data will be examined such as the assessment of general anxiety by the HADS questionnaire, a validated, standardized instrument, specifically designed for samples presenting with physical illness.¹⁸ Anxiety and depressive symptoms measured with HADS reflect true anxiety and depression symptomatology rather than the manifestations of somatic illness. In addition, the DS14 will be used to measure the time-dependent changes in anxiety for different personality types. Finally, the accuracy of PN will be ascertained by calculating its sensitivity and specificity.

The anticipated confirmation of a significant decrease in anxiety conferred by PN in this trial should spur further advances in

remote patient monitoring, with a view to further increase the patient acceptance of implanted devices, improve overall quality of life, and lower the incidence of device-related affective disorders.

Authors' contributions

F.D. and V.W. wrote the manuscript, which was reviewed and approved by all other authors. All authors have contributed to the design of the study. Rodolphe Ruffy, reviewed this manuscript for style and language.

Conflict of interest: F.D., P.D., S.F., C.P., and S.S.P. are members of the PANORAMIC Steering Committee and receive royalties or other research support from St. Jude Medical. V.W. is an employee of St. Jude Medical.

Funding

This study was funded by research grants from St. Jude Medical.

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